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EXAMINER

SZPERKA, MICHAEL EDWARD

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/518,701	Applicant(s) LEVINSON ET AL.	
	Examiner Michael Szperka	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-8,22-24,26-29,32-37 and 50-73 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-8,22-24,26-29,32-37 and 50-73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's response and amendments received November 13, 2008 are acknowledged.

Claims 4, 9-21, 25, 30, 31 and 38-49 have been canceled.

Claims 1, 5, 8, 22, 2628, 29, and 35 have been amended.

Claims 50-73 have been added.

Claims 1-3, 5-8, 22-24, 26-29, 32-37, and 50-73 are pending and are under examination in this office action.

Claim Objections

2. The objection to claims 5 and 35 for minor informalities has been withdrawn in view of applicant's claim amendments received November 13, 2008 which adequately address the formatting issue of record.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. The rejection of claims 1-3, 5-8, 22-24, 26-29, and 32-27 under 35 U.S.C. 102(a and e) as being anticipated by WO 02/20038 has been withdrawn in view of applicant's claim amendments received November 13, 2008.

Specifically, the claims have been amended to recite that a proteolytic cleavage sequence occurs between the IgE and helper T epitopes in the claimed constructs and this limitation is not disclosed in the '038 document.

5. The rejection of claims 1-3, 5-8, 22-24, 26-29, and 32-27 under 35 U.S.C. 102(a and e) as being anticipated by Klysner et al. (US2002/0172673 has been withdrawn in view of applicant's claim amendments received November 13, 2008.

Specifically, the claims have been amended to recite that a proteolytic cleavage sequence occurs between the IgE and helper T epitopes in the claimed constructs and this limitation is not disclosed in the '673 publication.

6. The rejection of claims 1-3, 22-24, and 28 under 35 U.S.C. 102(b) as being anticipated by Chen et al (WO 98/53843) has been withdrawn in view of applicant's claim amendments received November 13, 2008.

Specifically, the claims have been amended to recite that a proteolytic cleavage sequence occurs between the IgE and helper T epitopes in the claimed constructs and this limitation is not disclosed in the '843 document.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. The rejection of claims 5-8, 26, 27, 29, and 32-37 under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843) in view of Wang et al. (WO 99/67293) and in view of Hollis et al. (US 5,629,415) has been withdrawn in view of applicant's claim amendments received November 13, 2008.

Specifically, the claims have been amended to recite that a proteolytic cleavage sequence occurs between the IgE and helper T epitopes in the claimed constructs and the use of such cleavable linker sequences is not disclosed in the cited references.

9. Applicant's claim amendments received November 13, 2008 have successfully overcome all rejections and objections of record. However, the claim limitations newly presented as part of the November 13, 2008 response have necessitated the following new grounds of rejection.

10. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843, of record) in view of Wang et al. (WO 99/67293, of record) in view of Hollis et al. (US 5,629,415, of record) and in view of Rutter (US Patent 4,769,326, newly cited).

Chen et al. disclose vaccine constructs comprising the membrane bound domain of IgE coupled to heterologous sequences and excipients (see entire document, particularly the abstract and pages 3-5). These constructs are disclosed as being made recombinantly using vectors and host cells (see page 5). Note that heterologous antigens comprise helper T epitopes, and that Chen et al. disclose that their products are to be used in the suppression of IgE mediated responses, such as those that occur in allergy (see page 2).

The disclosure of Chen et al. differs from the instant claimed invention in that the nucleic acids of Chen et al. are not disclosed as being administered to a patient (i.e. the

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nucleic acids are not disclosed as a vaccine) nor are they disclosed as comprising a proteolytic cleavage sequence.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11, 13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes (see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Hollis et al. disclose that recombinant IgE encoding polynucleotides can be inserted in to plasmid vectors and used to generate a wide variety of host cells including bacterial and mammalian cells (see entire document, particularly columns 4-7). Such host cells can be used to express polypeptides, with antibodies specific for the IgE constructs being used for affinity purification of the expressed polypeptide (see column 7).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of Chen et al. to comprise promiscuous tetanus toxoid T helper epitopes so that they could be used in nucleic acid vaccines that would be effective in a majority of individuals in populations

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comprising diverse MHC haplotypes. Note that the use of nucleic acid vaccines was well known and routine in the art as disclosed by Wang et al. Such vaccines could be propagated in bacterial host cells as disclosed by Hollis et al. due to their ease of manufacture. A person of ordinary skill in the art would have been further motivated to incorporate proteolytic cleavage sequence linkers into such constructs since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

11. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 (of record) in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326, newly cited).

The '038 document discloses nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and pages 37 and 41). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly page 30). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly pages 52-56 and 66-67). The nucleic acids of the '038 document are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly pages 60-66). These teachings differ from the claimed invention in that they do not disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11, 13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes

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(see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of the '038 document to comprise proteolytic cleavage sequence linkers since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

12. Claims 1-3, 5-7, 22-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673, of record) in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326, newly cited).

Klysner et al. disclose nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and paragraphs 121 and 132). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly paragraph 101). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly paragraphs 171- 180 and 214-219). The nucleic acids of Klysner et al. are also disclosed as being present in bacterial and

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mammalian cells for use in production of recombinant polypeptides (see particularly paragraphs 198-213). This disclosure differs from the claimed invention in that Klysner et al. do not disclose the use of linkers comprising a proteolytic cleavage sequence between the epitopes.

Wang et al. disclose vaccine constructs wherein IgE sequence is coupled to T helper epitopes such as those from tetanus toxoid, and wherein the administered construct is a nucleic acid (see entire document, particularly the abstract and pages 11, 13-14, 16, 20, 39-40). T helper epitopes from tetanus toxoid are preferred because they comprise the advantageous property of being promiscuous T helper epitopes that can be recognized by most members of a population expressing diverse MHC haplotypes (see particularly pages 16, 17, and 33). Wang et al. further disclose the desirability of inserting a linker sequence between IgE and T helper epitopes, such linkers offering the advantage of disrupting artificial secondary structures that result from directly joining the C-terminus of one epitope directly to the N-terminus of the other epitope and the advantage of acting as a flexible hinge that allows for more effective interactions with immune cells (see particularly page 32).

Rutter discloses that the use of linkers comprising proteolytic cleavage sites is desirable in the manufacture of fusion constructs since said linkers allow for the efficient incorporation and removal of desired functional properties (see entire document, particularly the abstract). Such linkers allow for the separation the component parts of the fusion protein without otherwise causing degradation or proteolysis to the proteins or peptides of interest (see particularly columns 7, 8, 10, and 12).

Therefore, it would have been obvious to a person of ordinary skill at the time the instant invention was made to modify the nucleic acid constructs of Klysner et al. to comprise proteolytic cleavage sequence linkers since separation of epitopes provides the advantages of reduced unwanted secondary structure and increased flexibility as disclosed by Wang et al. and provides the advantage of allowing the component epitopes to be easily separated without excessive proteolytic degradation as disclosed by Rutter.

13. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (WO 98/53843, of record) in view of Wang et al. (WO 99/67293, of record) in view of Hollis et al. (US 5,629,415, of record) and in view of Rutter (US Patent 4,769,326, newly cited) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929, see entire document) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of Chen et al., Wang et al. Hollis et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype

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switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. Thus the "Ig leader" of Walls et al. is an "IgE leader".

14. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 (of record) in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326, newly cited). as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929, see entire document) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of the '038 document, Wang et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the

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time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. Thus the "Ig leader" of Walls et al. is an "IgE leader".

15. Claims 8, 32-37, 50, and 58-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673, of record) in view of Wang et al. (WO 99/67293, of record) and in view of Rutter (US Patent 4,769,326, newly cited) as applied to claims 1-3, 5-7, 22-24, and 26-29 above, and further in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929, see entire document) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The inventions rendered obvious by the disclosures of Klysner et al., Wang et al., and Rutter have been discussed above and differ from the claimed invention in that while they disclose the recombinant production of secreted polypeptides, they do not specify that the leader sequence used in such constructs is "an IgE leader sequence".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides. Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. Thus the "Ig leader" of Walls et al. is an "IgE leader".

16. Claims 8, 32-37, 50, and 66-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klysner et al. (US2002/0172673) in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929, see entire document) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

Klysner et al. disclose nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire document, particularly the abstract and paragraphs 121 and 132). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly paragraph 101). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly paragraphs 171- 180 and 214-219). The nucleic acids of Klysner et al. are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly paragraphs 198-213). This disclosure differs from the instant claimed invention in that it is not specified that the leader sequence sued for the expression of soluble polypeptides is and "IgE leader".

Walls et al. disclose vectors for the expression immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides of Klysner et al. Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being joined to an already rearranged variable domain. Thus the "Ig leader" of Walls et al. is an "IgE leader".

17. Claims 8, 32-37, 50, and 66-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/20038 (of record) in view of Walls et al. (Nucleic Acids Research, 1993, 21:2921-2929, see entire document) as evidenced by Janeway et al. (Immunobiology, 3rd edition, Garland Publications, 1997, pages 3:26-3:31).

The '038 document discloses nucleic acid molecules comprising the membrane anchoring region of B-cell bound IgE linked to a foreign T helper epitope (see entire

document, particularly the abstract and pages 37 and 41). Helper T epitopes are disclosed as coming from tetanus toxoid (see particularly page 30). These nucleic acids are further disclosed as being present in plasmids and viral vectors for use in vaccines comprising excipients (see particularly pages 52-56 and 66-67). The nucleic acids of the '038 document are also disclosed as being present in bacterial and mammalian cells for use in production of recombinant polypeptides (see particularly pages 60-66). This disclosure differs from the instant claimed invention in that it is not specified that the leader sequence used for the expression of soluble polypeptides is an "IgE leader".

Walls et al. disclose vectors for the expression of immunoglobulin polypeptides (see entire document, particularly the abstract). These vectors comprise the immunoglobulin (Ig) leader sequence. The Ig leader of Walls et al. comprises an intron which must be spliced out prior to translation (see particularly Figure 1, the last full paragraph on page 2924, and the paragraph spanning the left and right columns of page 2925). It is known that introns are essential for the efficient expression of Ig genes and that the presence of intronic sequences in expression vectors enhances expression of the inserted gene of interest (see particularly the bottom right column of page 2924).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make recombinant constructs, vectors and host cells comprising the Ig leader sequence disclosed by Walls et al. Motivation to do so at the time the invention was made comes from the teachings of Walls et al. that the Ig leader sequence encodes an intron and that the presence of introns is essential for efficient expression of Ig constructs, such as chimeric IgE polypeptides of the '038 document. Note that as evidenced by Janeway et al., immunoglobulin genes are assembled via the process of V(D)J recombination, and that different isotypes (i.e. IgG, IgE, IgA) are obtained by isotype switching. As such, the immunoglobulin heavy chain leader sequence is upstream of the rearranged variable domain (FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4) and thus an "IgE leader" is the same sequence as an IgM, IgD, IgG, and IgA leader sequence since the constant domain exons are not expressed without being

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joined to an already rearranged variable domain. Thus the "Ig leader" of Walls et al. is an "IgE leader".

18. No claims are allowable.

19. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

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